PHARMACEUTICAL PREPARATION CONTAINING GABAPENTIN

Description

The present invention relates to a pharmaceutical composition containing gabapentin.

Gabapentin is the common name of the 1-aminomethyl-cyclohexane-acetic acid, a known drug with anti-epileptic activity.

The drug is not protected by patent, nevertheless in the US patent n. 6.054.482 in the name of Gödecke AG stable pharmaceutical compositions of gabapentin are claimed which maintain, for one year at 25° C and 60% r. h., the content of the corresponding lactam (a known toxic product which can be generated by gabapentin by dehydration) lower than 0.5% by weight and which have a content of anions of mineral acids lower than 20 ppm.

In the same patent a series of additives, which have to be avoided in the composition because they favour the formation of lactam, is listed as well. They are: modified cornstarch, croscarmellose sodium, glyceric esters of behenic acid, copolymers of metacrylic acid (type A and C), anion-exchange resins, titanium dioxide, silica gel and PEG with low molecular weight.

On the contrary, in the US patent n. 6.531.509 in the name of Teva Pharmaceuticals Industries Ltd. it is reported that the invention described in the Gödecke AG patent mentioned above is wrong and that stable compositions of gabapentin can be obtained even when the content of anions of mineral acids in the latter is greater than 20 ppm.

However, no data are provided in this regard, nor the criteria for choosing suitable additives are shown.

In the patent application n. WO 02/26263 in the name of Sigmapharm stable compositions of gabapentin are described containing a stabilizer comprising a compound able to reduce the ionic strength, and at least 20 ppm of one anion of mineral acid.

The stabilizers belong to the following classes: volatile alcohols, non-volatile alcohols, non-volatile liquids, water miscible solids or liquids, immiscible solids or liquids, liquid or solid surface active agents, antioxidants, ketones or aldehydes.

Currently, gabapentin is proposed with different dosages and in two pharmaceutical forms for oral use: capsules and tablets.

Nevertheless, the industrial production of gabapentin tablets has several drawbacks due to

the difficulty of compressing the raw material.

Therefore, it is necessary to use the new granulation.

However, this procedure too is not deprived of practical problems since by granulating with water, under different experimental conditions and with different procedures, the formation of a hydrate is always obtained, with consequent loss in the original crystalline structure.

An industrial granulation with organic solvents puts some limitations by obliging to use particular plants to protect operators and environment.

Now we have found that the problems mentioned above are overcome by granulating gabapentin with PEG (polyethylene glycol) with a melting point comprised between 50 and 80°C.

Therefore, it is an object of the present invention a gabapentin granulate obtained by granulating gabapentin with PEG having a melting point comprised between 50 and 80°C.

The so-obtained granulate can be used as such for preparing tablets or it can be supplemented with other additives and then compressed.

If desired, it is also possible to add to gabapentin and to PEG, before the granulation, additives useful for the subsequent compression or for the disgregation of the tablet such as glydants or disgregants, specific examples being the silica gel, the pregelatinized starch and the croscarmellose sodium.

It is important noting that in the US patent n. 6.054.482 mentioned above said substances are included in the ones designated as destabilizing substances of the active principle. On the contrary, we have not noticed any significative degradation of gabapentin (calculated through the quantity of the lactam which has formed) when formulated starting from a granulate according to the present invention and when it contained less or more 20 ppm of an anion of a mineral acid.

Therefore, it is a second object of the present invention a gabapentin granulate obtained by granulating the gabapentin with PEG having the melting point comprised between 50 and 80°C and additives chosen among glydants, disgregants and diluents.

Preferably, and this constitutes an additional object of the invention, the granulate will contain a high quantity of gabapentin, for example higher than 80% by weight or even higher

than 90% by weight and it can reach even 98% by weight, the remaining 2% being the PEG. The usable PEG is the one commonly used in the pharmaceutical field and it is not necessary using particular pure PEGs. If desired, PEG mixtures with different average molecular weight can be used so that the melting point of the mixture is comprised between 50 and 80°C. Hereinafter under the PEG term, a single PEG or a PEG mixture having the melting point comprised between 50 and 80°C will be designated indifferently.

The granulate can be prepared by using rotogranulators available on the market, such as, for example, the fast rotogranulators (high shear mixer) produced by the Zanchetta firm, Rotojunion 10 model, or similar devices such as Glatt, Collette, Diosna.

The pharmaceutical compositions in tablets can be prepared by direct compression of the granulate or by adding to the granulate, before the compression, additives of typical pharmaceutical use which give to the tablet properties useful both in the industrial preparation and in the regular therapeutic effect of the drug administered therewith.

Examples of such additives are disgregants, lubricants and glydants.

Usually, when one wishes to add other additives to the granulate, the composition of the tablet resulting from the mixture compression will be comprised within the following values:

granulate	70-100% by weight, preferably 80-100%
additives	0-30% by weight, preferably 0-20%

Therefore, it is an object of the present invention gabapentin tablets containing between 70 and 100% by weight of a granulate as described above and between 0 and 30% by weight, preferably between 0 and 20% of additives for pharmaceutical use.

Since the granulate of the invention does not cause the degradation of the active principle and since one of the gabapentin pharmaceutical forms for oral use is constituted by capsules containing it, the granulate itself can be used successfully for the preparation of capsules.

Therefore, it is a further object of the present invention the use of the granulate as described above for the preparation of gabapentin capsules and the capsules containing it.

In order to better illustrate the present invention, the following examples are now provided.

Example 1

General procedure for the granulate preparation

A mixture of powders constituted by gabapentin, PEG and, in case, other additives is charged in a Zanchetta rotogranulator, Rotojunior 10 model.

The total amount of powders which can be charged in the apparatus mentioned above is comprised between 0.8 and 3 kg and 1-2 kg are preferably charged.

The powders are mixed in the rotogranulator for 5 minutes at 25°C, the blade speed being 100 rpm.

Then, the mixture under stirring is heated until the PEG melting point (between 50 and 80°C) with the blade speed comprised between 150 and 400 rpm, preferably 300 rpm, and the crusher speed comprised between 600 and 1200 rpm, preferably, 1000 rpm. It is left for a time comprised between 30 and 60 minutes, preferably 45 minutes.

The mixture is then cooled at 25°C by keeping it under stirring with the blade speed of 100 rpm and the crusher speed of 1000 rpm.

The so-obtained granulated is discharged which, independently from the quantity of the introduced materials, can have a composition comprised within the following values:

Gabapentin	70-98% by weight
PEG	2-25% by weight
Additives	0-20% by weight

the total being 100%.

Example 2

With the procedure described in the example 1 the granulates having the following composition have been prepared:

Gr 1

Gabapentin	90%
PEG 6000	6%
Modified cornstarch	4%

Gr 2

Gabapentin	88%
PEG 4000	2%
Modified cornstarch	10%

Gr 3

Gabapentin	90%
PEG 1500	1%
PEG 4000	4%
Croscarmellose sodium	5%

The so-produced granulates have optimum sliding and compressibility properties (rest angle 30-35% and Carr index 10-18%); the appearance of gabapentin degradation products is not found and, from the FT-Raman analysis, the gabapentin keeps its original crystalline form.

Example 3

The granulates according to the invention can be used for obtaining pharmaceutical tablets by using usual compressors.

The mixtures suitable for obtaining tables are comprised in the following values:

granulate	70-100% by weight
additives	0-30% by weight

Co 1

Gr 1 granulate (see example 2)	85%
pregelatinized starch	13.5%
colloidal silica	0.5%
stearate magnesium	0.5%
titanium dioxide	0.5%

Co 2

Gr 3 granulate	87%
croscarmellose sodium	11.5%
colloidal silica	0.5%
stearate magnesium	0.5%
titanium dioxide	0.5%

Co 2

Gr 2 granulate	85%
copolymer of the metacrylic acid (type C)	10%
stearate magnesium	0.5%
titanium dioxide	0.5%
glyceric esters of the behenic acid	4%

Co 4

The Gr 1 granulate described in the example 2 is compressed without adding additional additives to obtain tablets.

Co 5

Gr 1 granulate	99%
colloidal silica	0.5%
stearate magnesium	0.5%

Co 6

Gr 3 granulate	85%
PEG 4000	5%
copolymer of the metacrylic acid (type A)	10%

The so-obtained tablets show technological properties suitable for a pharmaceutical use (hardness 10-12 Kn, friability <0.1%, disgregation time comprised between 10 and 25', usually <15') and do not show degradation of the active principle or variations of the crystalline form. They are also suitable for a subsequent possible coating.

Example 4

The granulates identified as Gr 1 and Gr 2 in the example 2 have been used separately to fill-in gelatine capsulae by obtaining gabapentin pharmaceutical forms in capsules (Cap 1 and Cap 2). Similarly, capsules containing the following compositions have been prepared:

Cap 3

Gr 1 granulate	95%
cornstarch	4.5%

colloidal silica	0.5%
<u>Cap 4</u>	
Gr 3 granulate	98.5%
glyceril behenate	0.5%
colloidal silica	1%
<u>Cap 5</u>	
Gr 1 granulate	86%
croscarmellose sodium	10%
titanium dioxide	1%
cornstarch	4.5%